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10/697,399	10/30/2003	Jeffry D. Watkins	AME-08122	7480

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,399	WATKINS ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments filed 12 April 2004, and 22 December 2006, have been entered in full.

2. Claims 1-12 are canceled.

3. Claims 13-22 are pending.

Election/Restrictions

4. Applicant's election without traverse of Group III, claims 17-20 in the reply filed on 22 September 2006 is acknowledged. Furthermore, applicant's election of species A11 and VH2-5 is acknowledged. However, after further consideration the election of species is WITHDRAWN and all species will be examined.

5. Claims 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 21-22 are newly added and are drawn to the elected invention.

6. Claims 17-22 are under examination.

Specification

7. The disclosure is objected to because of the following reasons:

a. In the first sentence, the status of Application 10/110,141 needs to be updated to indicate that it is now allowed, and when it issues, with the correct patent number and the status of Application 09/434,870 needs to be updated to indicate that it is now US Patent 6,849,425.

b. On page 28, line 9, there is a typographical error where binding is misspelled "binging".

c. The incorporation by reference of the following sequences is improper: VH1-18, VH1-2, VH1-24, VH1-3, VH1-45, VH1-46, VH1-58, VH1-69, VH1-8, VH2-26, VH2-5, VH2-70, VH3-11, VH3-13, VH3-15, VH3-16, VH3-20, VH3-21, VH3-23, VH3-30, VH3-33, VH3-35, VH3-38, VH3-43, VH3-48, VH3-49, VH3-53, VH3-64, VH3-66, VH3-7, VH3-73, VH3-74, VH3-9, VH4-28, VH4-31, VH4-34, VH4-39, VH4-4, VH4-59, VH4- 61, VH5-51, VH6-1, VH7-81, A1, A10, A11, A14, A17, A18, A19, A2, A20, A23, A26, A27, A3, A30, A5, A7, B2, B3, L1, L10, L11, L12, L14, L15, L16, L18, L19, L2, L20, L22, L23, L24, L25, L4/18a, L5, L6, L8, L9, O1, O11, O12, O14, O18, O2, O4, O8, VI-11, VI-13, VI-16, V1- 17, VI-18, VI-19, V1-2, V1-20, V1-22, V1-3, V1-4, V1-5, V1-7, V1-9, V2-1, V2-11, V2-13, V2-14, V2-15, V2-17, V2-19, V2-6, V2-7, V2-8, V3-2, V3-3, V3-4, V4-1, V4-2, V4-3, V4- 15 4, V4-6, V5-1, V5-2, V5-4, V5-6. These sequences are deemed essential material, and essential material can only be incorporated by reference from a US Patent or US Patent application that does not incorporate the essential material by reference (see 37 CFR § 1.57). Additionally applicant is directed to MPEP 608.01(p) that states, in part,

> "37 CFR 1.57(f) addresses corrections of incorporation by reference by inserting the material previously incorporated by reference. A noncompliant incorporation by reference statement may be corrected by an amendment. 37 CFR 1.57(f). However, the amendment must not include new matter. Incorporating by reference material that was not incorporated by reference on filing of an application may introduce new matter. An incorporation by reference of essential material to an unpublished U.S. patent application,

> a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c). The improper incorporation by reference is not effective to incorporate the material unless corrected by the applicant (37 CFR 1.57(g)). Any underlying objection or rejection (e.g., under 35 U.S.C. 112) should be made by the examiner until applicant corrects the improper incorporation by reference by submitting an amendment to amend the specification or drawings to include the material incorporated by reference. A statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter is also required. 37 CFR 1.57(f). See also In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973)."

Furthermore, Applicant is directed to 37 CFR § 1.821, that discusses, "nucleotide and/or amino acid sequence disclosures in patent applications" to ensure sequence compliance for disclosed sequences.

d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

e. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

8. Claims 17-22 are objected to because of the following informalities:

Claim 17 has typographical errors in it as it recites human heavy chain genes that were not in the original claim. See VH-46, VH-18, VH-3-7 and VH-3-21, which were originally VH1-46, VH1-18, VH3-7 and VH3-21. The claims will be examined for the

originally filed VH1-46, VH1-18, VH3-7 and VH3-21 genes because these changes appear to be typographical errors.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 17-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 17-22 are vague and indefinite in the recitation of "A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8" as the sole means of identifying the light chain genes referred to in claim 17 and "VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51" as the sole means of identifying the heavy chain genes referred to in claim 17. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. For example, see US 20060217419 A1 that discloses compound A11 in paragraph [0395] and US 2000160071 A1 that discloses HLA-A allele A11 in paragraph [0083]. Amending the claims to specifically and uniquely identify A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, O8, VH2-5, VH2-

26, VH2-70, VH3-20, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51, for example, by SEQ ID NO would obviate this rejection, provided no new matter is introduced.

12. Claims 17-22 are vague and indefinite in the recitation of "CDR altered with respect to" in claims 17, 21, and 22. While it is clear from the specification on page 21 that altered refers to a change in amino acid sequence from the donor CDR, altered is a relative term and as such is vague and indefinite. Is the amino acid sequence altered by a substitution, an insertion, a deletion, or some combination of the three? Furthermore, is the amino acid sequence altered by random chemical mutagenesis, codon based mutagenesis, error-prone PCR or some other mutagenesis? Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 17-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2163).

Claims 17-22 are broadly drawn a method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region by providing framework region oligonucleotides from heavy and light chain genes selected from the sequences consisting of: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, O8, VH2-5, VH2-26, VH2-70, VH3-20, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 and providing altered CDR oligonucleotides to create heteromeric variable regions that have higher affinity than a donor heteromeric binding region. The specification describes providing altered CDR oligonucleotides and combining them with framework region oligonucleotides to create heteromeric variable regions that have higher affinity than a donor heteromeric binding region. However, the specification does not describe the structural elements of a gene present in these DNA sequences. For example, the specification does not describe the organization, location or actual DNA sequences of promoter and regulatory regions and introns, all

defining elements of a "gene". Furthermore, the structural elements of the sequences represented by A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, O8, VH2-5, VH2-26, VH2-70, VH3-20, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 are not adequately described. The specification does not provide the sequences that correspond to the recited designations, A11, etc and the mere recitation of "A11, etc" does not convey a common structure. Futhermore, the general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed, so one of ordinary skill in the art could not at once envisage the sequences denoted by A11, etc. Thus, the specification describes providing altered CDR oligonucleotides and combining them with framework region oligonucleotides to create heteromeric variable regions that have higher affinity than a donor heteromeric binding region, but does not describe a method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region by providing framework region oligonucleotides from heavy and light chain genes selected from the sequences consisting of: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, O8, VH2-5, VH2-26, VH2-70, VH3-20, VH1-46, VH3-9, VH3-66, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 and providing altered CDR oligonucleotides to create heteromeric variable regions that have higher affinity than a donor heteromeric binding region as claimed. The specification lacks information to lead one of skill in the art to understand that the applicant had

possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Priority

15. It is noted that this application is a CIP of 10/110,141 and 09/434,870. Applications 10/110,141 and 09/434,870 do not disclose using unvaried human germline framework genes. Therefore the priority date granted for the purpose of art rejections is deemed to be that of the present application, i.e., October 30, 2003.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mhashilkar et al (Human Gene Therapy 10:1453-1467, June 10, 1999), in view of Wu et al (Journal of Molecular Biology 294:151-162, November 19, 1999) and Kawasaki et al (European Journal of Immunology 31:1017-1028, published online March 21, 2001) and Matsuda et al (Journal of Experimental Medicine 188(11):2151-2162, December 7, 1998).

The claims are drawn to a method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing oligonucleotides that encode four unvaried germline light chain framework regions wherein three of the four unvaried germline light chain framework regions are from a human kappa light chain gene selected from: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 with oligonucleotides encoding light chain CDRs with at least one light chain CDR altered

with respect to the donor light chain CDRs, such that oligonucleotides comprising an unvaried human germline light chain framework with at least one or at least two altered light chain CDRs are generated and providing and mixing oligonucleotides that encode four unvaried germline heavy chain framework regions wherein three of the four unvaried germline heavy chain framework regions are from a human heavy chain gene selected from: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 with oligonucleotides encoding heavy chain CDRs with at least one heavy chain CDR altered with respect to the donor heavy chain CDRs, such that oligonucleotides comprising an unvaried human germline heavy chain framework with at least one or at least two altered heavy chain CDRs are generated. The method further comprises expressing the oligonucleotides that are generated and identifying a heteromeric variable region with higher affinity that the donor heteromeric variable region.

Mhashilkar et al teach a method of expressing a heteromeric variable region comprising an unvaried human light chain framework region, wherein three of the four framework regions are from the same framework gene, and light chain CDRs from donor light chain CDRs and an unvaried human heavy chain framework region, wherein three of the four framework regions are from the same framework gene, and heavy chain CDRs from donor heavy chain CDRs (see page 1455 and page 1459, right column and figure 6). Mhashilkar et al also teach that the heavy and light chain frameworks were "best matched" to the murine antibody from 1238 human heavy and

1041 light chain genes, respectively (see page 1459, right column) to humanize the murine antibody to minimize creating an immune response against the murine antibody (see page 1454, right column). Furthermore, Mhashilkar et al teach that only the heteromeric variable region with unvaried light and heavy chain frameworks was as active as the original murine antibody, while the less humanized versions were considerably less protective (see page 1461, right column). Mhashilkar et al do not teach that the light and heavy chain CDRs are altered to express a heteromeric binding region with higher antigen binding affinity and such a heteromeric variable binding region was identified or that three of the four unvaried light chain framework regions were selected from: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8, or that three of the four unvaried heavy chain framework regions were selected from: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51. These deficiencies are made up for in the teachings of Wu et al and Kawasaki et al and Matsuda et al.

Wu et al teach a method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing overlapping oligonucleotides that encode four varied germline light chain framework regions with oligonucleotides encoding variant light chain CDRs and donor light chain CDRs, such that oligonucleotides comprising a varied human germline light chain framework and at least one light chain variant CDR are generated and providing and mixing oligonucleotides that encode four varied germline heavy chain

framework regions with oligonucleotides encoding variant heavy chain CDRs and donor heavy chain CDRs, such that oligonucleotides comprising a varied human germline heavy chain framework and at least one heavy chain variant CDR are generated. (see page 154, right column and page 155, left column). Wu et al further teach expressing the oligonucleotides that are generated and identifying a heteromeric variable region with higher affinity than the donor heteromeric variable region and that the framework used for humanization was selected by screening human germline sequences to find the most homologous sequence (see table 1, figure 2 and page 153, left column and page 155, right column). Wu et al also teach that focused mutagenesis of CDRs is well-known in the art and has been used to improve by 90-fold the affintiy of a humanized anti-integrin complex (see page 152, right column).

Kawasaki et al teach human germline kappa light chain genes that are often screened to find the most homologous light chain sequence during humanization of an antibody, including: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 (see table 1 and abstract).

Matsuda et al teach human germline heavy chain genes that are often screened to find the most homologous heavy chain sequence during humanization of an antibody, including: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 (see table 2 and abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to "best match" the variable region of an antibody

with the human germline light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Mhashilkar, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, in order to express and identify antibodies that are less immunogenic in a clinical setting, i.e. they are humanized with a minimal number of murine amino acids, and have increased binding affinity, so they can target antigens better and be given in smaller doses to minimize side effects. Furthermore, it was known by those of ordinary skill in the art that murine antibodies are "best matched" with human framework sequences during the humanization process, as taught by Mhashilkar and Wu, so it would have been *prima facie* obvious to one of ordinary skill in the art to choose from the light chain genes A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 and to choose from the heavy chain genes VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51, the heavy and light chain gene that "best matched" the variable region being humanized and affinity matured.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to "best match" the variable region of an antibody with the human germline light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Mhashilkar, while

increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, and combine them into a one-step humanization and affinity-maturation process because segregating the processes of humanization can be time-consuming as taught by Wu (see page 152, right column). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to "best match" the variable region of an antibody with the human germline light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Mhashilkar, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, and combine them into a one-step humanization and affinity-maturation process in order to save time and decrease immunogenicity in the clinical setting. Furthermore, one of skill in the art would have had a reasonable expectation of success, because it was known in the art that a variable region with an unvaried framework can perform better than a heteromeric variable region with a varied framework as taught by Mhashilkar and focused mutagenesis of CDRs can create heteromeric variable regions with higher binding affinity than a donor heteromeric variable region as taught by Wu. Thus, there would be an advantage and a reasonable expectation of success in "best matching" the variable region of an antibody with human germline light chain genes and human germline heavy chain genes, in order to create a heteromeric variable region with an unvaried framework region, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with

overlapping oligonucleotides, and combining them into a one-step humanization and affinity-maturation proces, in view of Mhashilkar et al and Wu et al and Kawasaki et al and Matsuda et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al (The Journal of Immunology 169:1119-1125, July 15, 2002), in view of Wu et al (Journal of Molecular Biology 294:151-162, November 19, 1999) and Kawasaki et al (European Journal of Immunology 31:1017-1028, published online March 21, 2001) and Matsuda et al (Journal of Experimental Medicine 188(11):2151-2162, December 7, 1998).

The claims have been described *supra*.

Tan et al teach a method of expressing a heteromeric variable region comprising an unvaried human light chain framework region, wherein three of the four framework regions are from the same framework gene, and light chain CDRs from donor light chain CDRs and an unvaried human heavy chain framework region, wherein three of the four framework regions are from the same framework gene, and heavy chain CDRs from donor heavy chain CDRs (see abstract, page 1123, left column and page 1124, left column). Tan et al also teach that known human germline heavy and light chain variable regions were compared to the murine antibody in order to pick the light chain and heavy chain that would work best for humanization (see page 1122, left column).

Furthermore, Tan et al teach that germline-encoded antibodies are thought to be tolerated by the body better (see page 1120, right column). Tang et al do not teach that the light and heavy chain CDRs are altered to express a heteromeric binding region with higher antigen binding affinity and that such a heteromeric variable binding region was identified or that three of the four unvaried light chain framework regions were selected from: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8, or that three of the four unvaried heavy chain framework regions were selected from: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51. These deficiencies are made up for in the teachings of Wu et al and Kawasaki et al and Matsuda et al.

Wu et al has been described *supra.*

Kawasaki et al has been described *supra.*

Matsuda et al has been described *supra.*

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to compare the variable region of an antibody with the human germline light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Tan, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, in order to express and identify antibodies that are less immunogenic in a clinical setting, i.e. they are humanized with a minimal number of

murine amino acids, and have increased binding affinity, so they can target antigens better and be given in smaller doses to minimize side effects. Furthermore, it was known by those of ordinary skill in the art that murine antibodies are compared with human framework sequences during the humanization process, as taught by Tan and Wu, so it would have been *prima facie* obvious to one of ordinary skill in the art to choose from the light chain genes A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 and to choose from the heavy chain genes VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51, the heavy and light chain gene that was most similar to the variable region being humanized and affinity increased.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to compare the variable region of an antibody with the human germline light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Tan, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, and combine them into a one-step humanization and affinity-maturation process because segregating the processes of humanization can be time-consuming as taught by Wu (see page 152, right column). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to compare the variable region of an antibody with the human germline

light chain genes taught in Kawasaki and the human germline heavy chain genes taught in Matsuda, in order to create a heteromeric variable region with the unvaried framework of Tan, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with the overlapping oligonucleotides of Wu, and combine them into a one-step humanization and affinity-maturation process in order to save time and decrease immunogenicity in the clinical setting. Furthermore, one of skill in the art would have had a reasonable expectation of success, because it was known in the art that focused mutagenesis of CDRs can create heteromeric variable regions with higher binding affinity than a donor heteromeric variable region as taught by Wu and Tan (see page 1124, right column). Thus, there would be an advantage and a reasonable expectation of success in comparing the variable region of an antibody with human germline light chain genes and human germline heavy chain genes, in order to create a heteromeric variable region with an unvaried framework region, while increasing the binding affinity of the heteromeric variable region by just altering the CDRs with overlapping oligonucleotides, and combining them into a one-step humanization and affinity-maturation process, in view of Tan et al and Wu et al and Kawasaki et al and Matsuda et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 17-22 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 39-42 of copending Application No. 10/697,400, in view of Kawasaki et al (European Journal of Immunology 31:1017-1028, published online March 21, 2001) and Matsuda et al (Journal of Experimental Medicine 188(11):2151-2162, December 7, 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims only differ slightly in scope.

The instant claims have been described *supra*.

Claims 39-42 of copending Application No. 10/697,400 are drawn to method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing oligonucleotides that encode four unvaried germline light chain framework regions with oligonucleotides

encoding variant light chain CDRs and donor light chain CDRs, such that oligonucleotides comprising an unvaried human germline light chain framework and at least one light chain variant CDR are generated and providing and mixing oligonucleotides that encode four unvaried germline heavy chain framework regions with oligonucleotides encoding variant heavy chain CDRs and donor heavy chain CDRs, such that oligonucleotides comprising an unvaried human germline heavy chain framework and at least one heavy chain variant CDR are generated. The method further comprises expressing the oligonucleotides that are generated and identifying a heteromeric variable region with higher affinity than the donor heteromeric variable region. The claims in copending Application No. 10/697,400 do not teach that the framework regions of the light chain gene should be selected from: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8, or that the heavy chain genes should be selected from: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51. These deficiencies are made up for in the teachings of Kawasaki et al and Matsuda et al.

Kawasaki et al has been described *supra*.

Matsuda et al has been described *supra*.

The claims in the instant application are obvious variants of claims 39-42 of copending Application No. 10/697,400 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to align the antibody being humanized and affinity matured with the unvaried germline light chain

genes, A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 and the unvaried germline heavy chain genes, VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51, in order to maximize the probability of generating a functional humanized antibody with minimal immunogenicity.

One of ordinary skill in the art would have been motivated to align the antibody being humanized and affinity matured with the unvaried germline light chain genes, A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 and the unvaried germline heavy chain genes, VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 and pick the set the "best matches" the antibody being humanized and combine it with the method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing oligonucleotides that encode four unvaried germline light chain framework regions with oligonucleotides encoding variant light chain CDRs and donor light chain CDRs, such that oligonucleotides comprising an unvaried human germline light chain framework and at least one light chain variant CDR are generated and providing and mixing oligonucleotides that encode four unvaried germline heavy chain framework regions with oligonucleotides encoding variant heavy chain CDRs and donor heavy chain CDRs, such that oligonucleotides comprising an unvaried human germline heavy chain

framework and at least one heavy chain variant CDR are generated of copending Application No. 10/697,400, in view of Kawasaki et al and Matsuda et al, because Matsuda et al teach that human germline framework variable sequences are "useful in designing humanized antibodies" (page 2152, left column). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing oligonucleotides that encode four unvaried germline light chain framework regions with oligonucleotides encoding variant light chain CDRs and donor light chain CDRs, such that oligonucleotides comprising an unvaried human germline light chain framework and at least one light chain variant CDR are generated and providing and mixing oligonucleotides that encode four unvaried germline heavy chain framework regions with oligonucleotides encoding variant heavy chain CDRs and donor heavy chain CDRs, such that oligonucleotides comprising an unvaried human germline heavy chain framework and at least one heavy chain variant CDR are generated of copending Application No. 10/697,400 with the germline heavy and light chain genes taught by Kawasaki et al and Matsuda et al in order have the best chance of producing a functional humanized antibody. Furthermore, one of skill in the art would have had a reasonable expectation of success, because it was known that during the humanization process that antibodies are "best matched" to multiple heavy and light chain genes and the gene that "best matches" the antibody being humanized is selected for the humanization process. Thus, there would be an advantage and a reasonable

expectation of success in using the method of expressing a heteromeric variable region having higher antigen binding affinity than a donor heteromeric variable region, comprising providing and mixing oligonucleotides that encode four unvaried germline light chain framework regions with oligonucleotides encoding variant light chain CDRs and donor light chain CDRs, such that oligonucleotides comprising an unvaried human germline light chain framework and at least one light chain variant CDR are generated and providing and mixing oligonucleotides that encode four unvaried germline heavy chain framework regions with oligonucleotides encoding variant heavy chain CDRs and donor heavy chain CDRs, such that oligonucleotides comprising an unvaried human germline heavy chain framework and at least one heavy chain variant CDR are generated of copending Application No. 10/697,400 with the germline light chain genes, A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L6, L8, O12, O2, and O8 and the germline heavy chain genes, VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VH1-46, VH3-9, VH3-66, VH3-72, VH3-74, VH4-31, VH1-18, VH1-69, VH3-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51 in order to humanize an antibody, in view of claims 39-42 of copending Application No. 10/697,400 and Kawasaki et al and Matsuda et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 17-22 are directed to an invention not patentably distinct from claims 39-42 of commonly assigned application 10/697,400. Specifically, see the discussion above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned application 10/697,400, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
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David Blanchard
AU 1643